Cell transplantation strategies for acquired and inherited disorders of peripheral myelin.

Journal: Ann Clin Transl Neurol

Publication Year: 2018

Authors: A K M G Muhammad, Kevin Kim, Irina Epifantseva, Arwin Aghamaleky-Sarvestany, Megan E Simpkinson, Sharon Carmona, Jesse Landeros, Shaughn Bell, John Svaren, Robert H Baloh

PubMed link: 29468179

Funding Grants: Human iPSC modeling and therapeutics for degenerative peripheral nerve disease

Public Summary:
Disease of peripheral nerve cause significant disability, and result from a variety of causes including nerve injury, metabolic disorders, immune mediated damage, and genetic disorders. Few effective treatments exist for peripheral nerve disorders, and in many cases replacement of damaged protective cells (termed Schwann cells) would be desirable. Schwann cells generate myelin which ensheaths long projecting axons from the nervous system out to the muscles, skin and other tissues. However in the context of non-traumatic neuropathies, therapeutic cell transplantation has not been demonstrated. Here we showed that Schwann cells could successfully be transplanted into two different models of damage to peripheral nerve, and migrate sufficiently to protect local axons. Lastly we showed that human induced pluripotent stem cells could be used to generate precursors to Schwann cells, and successfully transplanted into rat peripheral nerves. These results suggest that cell transplantation strategies are feasible for inherited and acquired diseases of peripheral nerve in humans.

Scientific Abstract:
Objective: To investigate transplantation of rat Schwann cells or human iPSC-derived neural crest cells and derivatives into models of acquired and inherited peripheral myelin damage. Methods: Primary cultured rat Schwann cells labeled with a fluorescent protein for monitoring at various times after transplantation. Human-induced pluripotent stem cells (iPSCs) were differentiated into neural crest stem cells, and subsequently toward a Schwann cell lineage via two different protocols. Cell types were characterized using flow cytometry, immunocytochemistry, and transcriptomics. Rat Schwann cells and human iPSC derivatives were transplanted into (1) nude rats pretreated with lysolecithin to induce demyelination or (2) a transgenic rat model of dysmyelination due to PMP22 overexpression. Results: Rat Schwann cells transplanted into sciatic nerves with either toxic demyelination or genetic dysmyelination engrafted successfully, and migrated longitudinally for relatively long distances, with more limited axial migration. Transplanted Schwann cells engaged existing axons and displaced dysfunctional Schwann cells to form normal-appearing myelin. Human iPSC-derived neural crest stem cells and their derivatives shared similar engraftment and migration characteristics to rat Schwann cells after transplantation, but did not further differentiate into Schwann cells or form myelin. Interpretation: These results indicate that cultured Schwann cells surgically delivered to peripheral nerve can engraft and form myelin in either acquired or inherited myelin injury, as proof of concept for pursuing cell therapy for diseases of peripheral nerve. However, lack of reliable technology for generating human iPSC-derived Schwann cells for transplantation therapy remains a barrier in the field.